

Sleep-Disordered Breathing and Cerebrovascular Disease

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Introduction

Sleep apnea syndrome (SAS) has broken free of the traditional paradigm for its clinical presentation (snoring, apnea, and somnolence), crossing over into a fascinating but difficult terrain to conquer: the question of its role in cardiovascular risk. In this line, recent studies have supported the relation between SAS—or rather, sleep-disordered breathing (SDB)—and cardiovascular risk, especially in the case of hypertension.¹⁻³ The findings of these studies are quite consistent, after correction for known confounders, and even point to beneficial effects on blood pressure of treatment with nasal continuous positive airway pressure (CPAP).⁴ Various pathophysiological mechanisms may be involved in this relation between SDB and cardiovascular risk. The hypoxemia associated with SDB may induce increased thrombogenicity triggered by plaque activation and act as an atherogenic factor, fracturing vulnerable plaques. Cardiovascular structural changes are also observed, such as ventricular hypertrophy and alteration of vascular tone regulating systems which, in turn, depend on myogenic and neurogenic factors (changes in sympathetic adrenergic activity due to arousal), humoral factors (concentrations of catecholamines, arginine-vasopressin, and natriuretic peptide), and local vascular wall factors (synthesis of endothelin, nitric oxide, and prostaglandin).⁵ These studies also explain the relation between SDB and ischemic cardiopathy or heart failure as well as the prognostic influence of SDB for them.^{6,7}

If we accept that SDB has an effect on the cardiovascular system, it would be surprising if cerebral circulation were to remain unaffected, as the brain and circulation are so closely related.

Several studies have indicated that certain tumoral and ischemic lesions in the brain, especially in the

brainstem, can give rise to respiratory problems when an individual is awake or asleep—the main problems being central apneas and Cheyne-Stokes periodic respiration.^{8,9} Without dismissing the relevance of these phenomena (we do not know their prognostic value although they seem to be associated with strokes accompanied by extensive hemispheric lesions and, therefore, with worse prognosis), we will focus mainly on SDB (predominantly obstructive in nature) with the hypothesis that such breathing favors the appearance of ischemic stroke and that it is ischemic stroke that fosters the appearance of central phenomena such as central apneas and Cheyne-Stokes respiration. This hypothesis appears simplistic, however, if we consider that the presence of periodic respiration destabilizes the upper airways and may give rise to obstruction.¹⁰ It would also be reasonable to think that the stroke itself, depending on its location, may cause obstructive apnea by affecting the motor function of the upper airway muscles, which would be rendered incompetent for maintaining the airway open under negative inspiratory pressure, therefore giving rise to obstructive events.

We will analyze the existing evidence of the relation between SDB and cerebrovascular disease in various contexts: *a*) evidence of its relation as a risk factor; *b*) pathophysiological mechanisms that may explain this relation; *c*) evidence that SDB constitutes a prognostic factor, and *d*) evidence of the efficacy of CPAP treatment.

SDB as a Risk Factor for Stroke

Few epidemiological studies totally support the hypothesis that SDB is a risk factor for stroke. However, data from the Sleep Heart Health Study¹¹ show, for the appearance of stroke, an odds ratio of 1.58 for an apnea-hypopnea index (AHI) greater than 11. This is the only epidemiological datum on a large scale available to us, although some evidence can be found from other studies with a variety of methodologies, including case-control studies, and with polysomnographic analyses of varying complexity. Home use of portable respiratory screening polygraphs on the headboard of the patient's bed has enabled the study of a greater number of patients, earlier

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on after the onset of symptoms, than was possible with conventional polysomnography, which involves going to a sleep unit, thus posing logistical difficulties for patients who often are confused and agitated. Although most studies have been carried out with small numbers of patients and do not always control for all confounding factors, they have all obtained results that point in the same direction: toward a much lower prevalence of SDB among control patients who have not experienced stroke (on the order of 18%) than among stroke victims (70%) who were matched for age and sex (Table).¹²⁻²² The SDB prevalence for patients who have experienced a stroke is higher than that expected for subjects of similar ages, although the figures should be set in the context of an expectation of higher prevalence among those over 65.²³ When our group of researchers carried out a study on 161 patients who had had either a stroke or a transient ischemic attack (TIA), performing respiratory polysomnography during the acute phase and again after 3 months, during the stable phase, we found a high prevalence of SDB, as shown in other studies, with approximately 72% of the patients having an AHI greater than 10 and 28% having an AHI greater than 30.¹⁹ These figures were much higher than those observed for equivalent age groups in the epidemiological study by Duran et al²⁴ in Vitoria. We noted an unusually high frequency of central events (central apnea and Cheyne-Stokes respiration) but were unable to establish any relation to the topography of the stroke. Furthermore, we observed a significant decrease in the AHI during the stable phase that can be accounted for by a reduction in central events and in Cheyne-Stokes respiration. Two subsequent studies obtained similar results.^{22,25} From those findings we might hypothesize that 2 types of SDB are observed in stroke: obstructive events, which do not usually vary and which probably precede the stroke, thus constituting a risk factor; and central SDB, which would be secondary to the stroke as suggested by the fact that central apneas decrease during the stable phase. Consequently, the question of whether SDB is a cause or a consequence of the stroke could be argued from either hypothesis.

Supporting the hypothesis that SDB precedes the stroke would be the patient's previous history of SAS, the presence of SDB in both stroke and TIA patients¹⁷ (with no apparent damage to the cerebral parenchyma²⁶), the lack of an association between SDB and the location of stroke, and the association between stroke occurrence at night and a high AHI.²⁷ However, factors such as the improvement of the AHI during the post-stroke phase, evidence that the stroke may exacerbate a preexisting SAS,²⁵ and the lack of AHI differences in patients with daytime and nighttime strokes²⁸ would favor the hypothesis that SDB is secondary to stroke.

Noteworthy in our own study was the fact that a decrease in the AHI during the stable phase also occurred among the TIA patients, which may be related to the fact that 36% of patients diagnosed with TIA present persistent cerebral ischemia despite total functional recovery.²⁶

Pathophysiologic Mechanisms Linking Stroke to SDB

Various mechanisms have been suggested to explain the influence of SDB on cardiovascular risk.⁵ Hypertension alone would offer a plausible explanation of the link between stroke and SDB, as hypertension is one of the main risk factors for stroke. Controlling hypertension would decrease the risk of stroke by 56%.²⁹ Numerous studies have proposed other SAS-related mechanisms that could lead to stroke. For example, high fibrinogen concentrations in stroke patients have been described as being proportional to their high AHIs, with a consequent increase in blood viscosity, which is considered a cardiovascular risk factor.³⁰ Moreover, CPAP treatment of these patients has resulted in a reduction of fibrinogen.³¹ SAS patients have also shown decreased cerebrovascular reactivity to hypercapnia compared to controls, and this can be interpreted as a decrease in the reserve capacity of cerebral circulation to meet diverse metabolic demands. This condition was corrected with CPAP, just as that of

TABLE
Studies Analyzing Sleep-Disordered Breathing in Stroke Patients*

Authors	Sample Size	Age (Years) [†]	Diagnostic Method	Days Since Stroke	Onset AHI (Events/Hour) [‡]	AHI ≥10	AHI ≥30
Kapen et al ¹²	47	62	PSG		28.2		
Mohsenin ¹³	10	56	PSG		52		
Good et al ¹⁴	19		PSG	18	35.6	95%	53%
Dyken et al ¹⁵	24	65	PSG	16	26	71%	37.5%
Bassetti and Aldrich ¹⁷	48	60	PSG	9	32	58%	
Parra et al ¹⁹	161	72	RPSG	2-3	21.2	71.4%	28%
Davies et al ²⁰	46	68	RPSG	90		41%	
Wessendorf et al ²¹	147	61	PSG	46	34	43.5%	
Harbison et al ²²	34	74	RPSG	9		94%	
Hui et al ²⁵	51	64.2	PSG	3	23	67%	
Iranzo et al ²⁷	50	66.8	PSG	1	27.7	62%	

*AHI indicates apnea-hypopnea index; PSG, polysomnogram; RPSG, respiratory polysomnogram.
[†]Values are means.

elevated levels of fibrinogen was.³² Studies measuring cerebral circulation by transcranial Doppler sonography have shown marked variations in cerebral blood flow rates during apnea, a possible cofactor for cerebral ischemia, perhaps acting on arteries previously affected by atheromatosis.³³

Other pathophysiological mechanisms that may be involved are cardiac arrhythmias that occur during apnea,³⁴ enlargement of the intima-media in strokes accompanied by SAS,³⁵ atherosclerosis and stenotic artery disease,³⁶ and increased homocysteine plasma concentrations.³⁷

SDB as a Prognostic Factor for Stroke

Discussing the role of SDB in prognosis would require us to have information about the functional recovery of stroke patients with SDB and the rates of stroke recurrence and/or mortality. However, the literature contains very little such information on which to base prognoses. Spriggs et al³⁸ show higher mortality in post-stroke patients with greater snoring intensity. Good et al¹⁴ describe poorer post-stroke functional recovery in patients with SAS. The same authors showed a single correlation between the number of oxygen desaturations and mortality within 1 year. Likewise, Dyken et al¹⁵ report a higher 4-year mortality rate among stroke patients with SAS. The presence of SDB is also associated with early neurological deterioration but not with degree of neurological deterioration at 6 months.²⁷

Our group analyzed 2-year survival in a series of 161 stroke patients using a Cox multivariate regression model. Univariate analysis indicated that the patients who died had a significantly higher AHI than did the survivors. The multivariate model selected 4 predictor variables—age, ischemic heart disease, middle cerebral artery involvement, and AHI. The hazard ratio for the AHI was 1.05—indicating a 5% increased risk of dying and of dying sooner for every AHI increase of 1 point, adjusted for the remaining variables that were selected.³⁹ Aside from studies validating the model and looking at the magnitude of influence of prognostic factors, these are the only existing data on the relation between SDB and stroke; thus, larger studies are needed.

Nasal Continuous Positive Airway Pressure for Treating Patients With Sleep-Disordered Breathing and Stroke

Since the literature indicates that SDB may be a risk factor for stroke and may also affect the prognosis of stroke patients in terms of functional recovery and risk of death, it only follows that we should consider the potential utility of treatment with CPAP, which is known to be effective in treating SAS.⁴⁰ Moreover, we have seen that CPAP may act on some of the

pathophysiological mechanisms involved in SDB and, more specifically, SAS.^{31,32} Following are some of the questions posed regarding the possible effectiveness of CPAP treatment for SDB patients: Does the treatment improve functional recovery? Does it improve quality of life? Does it decrease morbidity? At what point should it be initiated? Is it feasible for SDB patients? What is the efficacy for this group of patients?

Such questions are numerous, but concrete answers are as few as the number of studies dealing with the subject of treatment—probably due to the difficulties implicit in a study of patients with aphasia, cognitive disorders, and motor impairment of varying degree. Three studies have attempted to answer some of the questions posed above. Although these studies are methodologically deficient, they have the merit of having approached the issue of treatment, thus opening the way for further investigation. Wessendorf et al⁴¹ showed an improvement in the subjective well-being of patients treated with CPAP as well as an improvement in night-time blood pressure, converting nondippers (<10% fall in blood pressure during the night) into dippers (≥10% fall in blood pressure during the night). A second study, by Sandberg et al,⁴² showed an improvement in symptoms of depression, considered a prognostic factor for stroke patients. Both studies rated adaptation and efficacy at approximately 50%,^{41,42} which is not significantly different from percentages for SAS patients treated conventionally. The same authors listed age, cognitive impairment, aphasia, low Barthel Index, and facial paralysis as factors that limit efficacy. In contrast to these findings are other, less optimistic, experiences. Hui et al²⁵ analyzed the feasibility of CPAP treatment, showing that 16 out of the 34 patients studied tolerated a single night of treatment and that only 4 out of 34 continued treatment after they were discharged, with a monthly average of 2.5 hours per day. There is, however, a fundamental difference between the first 2 studies and the latter. Wessendorf et al⁴¹ and Sandberg et al⁴² analyzed the treatment of patients in rehabilitation units during the stable phase of stroke, whereas Hui et al²⁵ analyzed treatment during the acute phase. Harbison et al⁴⁴ also reported their experience of attempting to treat patients in the acute phase, finding 0% tolerance, which forced them to discontinue the study. One of the main criticisms of studies of CPAP is the absence of placebo control groups. Although a design involving a sham CPAP treatment⁴⁵ would be methodologically more convincing, such a design would call for careful consideration since it involves patients who, as we have stated, present exceptional difficulties.

As to when to initiate treatment, it would seem appropriate in theory to begin during the acute phase in order to preserve the so-called “ischemic shadow” zone—areas of the cerebral parenchyma with ischemia, but without necrosis, whose preservation depends partly on functional recovery during the acute phase of the episode. It is on this “ischemic shadow” that pathophysiological disorders (oxygen desaturation, etc.)

accompanying apnea could have a negative effect.^{27,44} That hypothesis would seem to indicate greater potential benefit of CPAP treatment even though feasibility has yet to be demonstrated.

Conclusions

There seems to be an interrelation between SDB and cerebrovascular risk, although many aspects of the relation remain to be explored. Both prevalence data and the results of experimental studies indicate an independent role for SDB as a risk factor. However, even though the evidence suggests that SDB precedes or is an eventual cause of strokes, it is not impossible for the opposite to be true, for SDB to arise from stroke. In any case, neither possibility excludes the other. The phenomena observed after a stroke are probably a combination of pre-stroke alterations and post-stroke consequences. From the perspective of clinical repercussions, SDB probably influences functional recovery and mortality. Even if this influence is limited, it is important to identify and quantify SDB for patients with cerebrovascular disorders, given their social, economic and public health consequences. Likewise, it is important to determine the potential benefit of CPAP treatment.

From a practical perspective we could define the stroke patient with SDB as one who does not present with somnolence, has a moderately high AHI, exhibits central phenomena, and who shows low tolerance for CPAP treatment. The lack of somnolence leads us to question the need for CPAP treatment according to current recommendations. We doubt whether these patients, who have presented with a cerebrovascular event and SDB but no somnolence, could benefit from CPAP treatment. The effect of such treatment on these patients is particularly difficult to demonstrate due to their exceptional difficulties, and only multicenter studies could provide samples large enough to lead to valid conclusions.⁴⁶

Given the present situation, it seems prudent to ask key questions to rule out SDB when taking the history of a stroke or TIA patient. If SDB is suspected, logically it should be investigated, and a respiratory polysomnogram would be a sufficient step to take. If SAS is clearly present, treatment would then be indicated. If classical SAS is not present, then individualized treatment may be a possibility, but to write more concrete guidelines we will have to wait for future results that demonstrate a clear benefit of treatment.

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